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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/689,865	10/20/2003	Che-Ming Teng	16127-002003	3339
26161	7590	05/22/2006	EXAMINER	
FISH & RICHARDSON PC P.O. BOX 1022 MINNEAPOLIS, MN 55440-1022			BERNHARDT, EMILY B	
			ART UNIT	PAPER NUMBER
			1624	
DATE MAILED: 05/22/2006				

Please find below and/or attached an Office communication concerning this application or proceeding.

**Office Action Summary**

Application No.

10/689,865

Applicant(s)

TENG ET AL.

Examiner

Emily Bernhardt

Art Unit

1624

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 03 March 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-30 is/are pending in the application.
- 4a) Of the above claim(s) 1-13 and 23-30 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 14-22 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)  
Paper No(s)/Mail Date 1/15/04 & 4/7/05.
- 4) ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date. \_\_\_\_\_.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: \_\_\_\_\_.

Applicant's election without traverse of III in the reply filed on 3/3/06 is acknowledged.

However, in view of the many differing permutations present within A and Z variables based on bond attachment to the piperazine~~azine~~ ring which are variously classified as set forth above, as well as differing issues of patentability that exist for compounds within elected Group III as evidenced by the art of record such as Shimazaki or Kanoh, Group III has been further restricted as set forth below:

IIIA. Claims 14-22 drawn to compounds where Z is attached by way of a double bond to the piperazine~~azine~~ ring and A is attached by way of a single or double bond;

IIIB. Claims 14 and 23-30 drawn to compounds where Z is attached by way of a single bond to the piperazine~~azine~~ ring and A is attached by way of a single or double bond;

Applicants' elected species (compound 9) falls within Group IIIA.  
Applicants are advised that the claims will only be examined with respect to Group IIIA subject matter.

Claims 14-20 and 23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

1. In claim 14 mention is made of “linked to B” however no “B” variable is present in the structure shown in the claim. Perhaps “C” was really intended.

2. The proviso appearing in the  $R^a$  definition lacks antecedent basis as the superscripts  $R^d$  and  $R^d$  do not appear in the  $R^3$  definition several lines above.

Claims 14-20 and 22 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Specification is not adequately enabled for the scope of piperazinediones claimed which can carry a variety of functional groups at  $R^a$ ,  $R^b$ ,  $R^{a'}$ ,  $R^{b'}$  including nonlimiting scope of heterocycloalkyls and heteroaryls both directly and indirectly attached to the piperazine ring. Additionally these rings can be further substituted with a list of substituents that in turn can contain more hetero rings or acyls of nonlimiting scope or any carboxylate ester groups. The same applies for the scope of alkyl, cycloalkyl, aryl and arylalkoxy moieties

wherever they appear such as in R1/R2/R3 definitions or Ra/Rb/ Rb'/Re/Rf/Rg which can carry the same scope of substituents from a reading of the specification on p.3. Note In re Surrey 151 USPQ 724 regarding sufficiency of disclosure for a Markush group. Also see MPEP 2164.03 for enablement requirements in cases directed to structure-sensitive arts such as the pharmaceutical art.

Also note the criteria for enablement as set out in In re Wands cited in MPEP 2164.01(a), August 2000 edition, which includes factors such as:

1) Breadth of the claims- the claims cover compounds easily in the millions as pointed out above;

2) Level of unpredictability in the art- the invention is pharmaceutical in nature as it involves inhibition of angiogenesis- a complicated biological process which involves dealing/interfering with the presence of angiogenic activators such as VEGF, basic fibroblast growth factor and inhibitors such as thrombospondin, angiostatin in order to be successful in reaching the primary and metastatic site of a tumor. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved" and physiological activity is generally considered to be unpredictable. See In re Fisher 166 USPQ 18;

3) Direction or guidance- the compounds made and indicated as tested are not representative of the instant scope but are closer to each other than to

remaining scope having as Ra mainly phenyl unsubstituted or substituted with OH, halo, alkoxy or benzyloxy groups with fewer examples of unsubstituted pyridinyl, thienyl, furyl or indolyl with Rb being H with remaining moieties if present at R1/R2 being mainly H or acetyl and Re/Rf being H and R3 when aryl, phenyl;

4) State of the prior art- The compounds are piperazinedione derivatives substituted at the 3- and 5- positions with one of these requiring a very specific pattern- see  $R_3O-Ar-C(R^e)$  requirement- while the other end can vary from H, alkyl to having carbocyclic and hetero rings of non-limiting scope. While such compounds are known as evident from the art applied below, they are directed to only a small part of applicants' scope and thus do not evidence the many structural permutations permitted in the instant scope are known in the prior art for the same activity relied on herein;

5) Working examples- The test data presented in examples 36-38 is scant as no actual data is reported only wording such as large number showed inhibition of HUVEC proliferation in eg.36 or most inhibited VEGF inhibition in eg.37 and out of 6 compounds tested in eg.38, 4 showed ID50 values less than 3mg/kg in mice and thus no clear evaluation of which functional groups at various positions out of the many claimed might affect potency to a large or small degree.

In view of the above considerations, this rejection is being applied.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 14 –22 are rejected under 35 U.S.C. 102(b) as being anticipated by Teng (WO'858). The WO publication which corresponds to parent published more than a year from applicants' filing date. It describes many compounds within the instant scope for use as antitumor agents. See species appearing on p.4 which includes a species (2<sup>nd</sup> one) within claim 21. All of these species have double bonds at the 3- and 6-positions.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claim 22 is rejected under 35 U.S.C. 103(a) as being unpatentable over Teng. Claim 22 requires that the "A" link be attached by way of a single bond with "Z" attached by way of a double bond. While species in Teng do not

anticipate the instant scope Teng also teaches that the bonds can be double or single at this position. See main formula on p.3. Thus it would have been obvious to one skilled in the art at the time the instant invention was made to modify the species in Teng pointed out in the above 102 rejection by replacing a double bond with a single bond and in so doing obtain compounds within the instant scope for treating one or more tumor types.

It is recognized applicants are claiming 120 benefit of earlier parent of which instant case is a CIP. However benefit cannot be granted for more than one reasons. Subject matter covered by the present claims are not entirely described in earlier parent- compare R<sup>a</sup> as benzo[1,3]dioxol-yl as well as scope of substituents recited in specification on p.3 such as alkynyl, cycloalkenyl, arylthio, acyl, acyloxy, carboxylic ester as well as scope of heteroaryl which in the present case is not limited to a particular type of hetero atom(s) as ring members. However for 120 benefit there must be compliance with 35 USC 112 (description and enablement) as was set forth in *In re Scheiber* 199 USPQ 782; *In re Lukach* 169 USPQ 795; *In re Chu* 36 USPQ 2d 1089. Additionally, the claims do not comply with 35 USC 112, par.one for the reasons set forth in the above rejection.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A



nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 14-21 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims of U.S. Patent No. 6,635,649.

Although the conflicting claims are not identical, they are not patentably distinct from each other because subject matter claimed herein is also covered in part by the claims in the US patent which corresponds to applicants' parent.

US'649 has the same inventive entity as herein and issued after applicants' US filing date and thus only the WO equivalent is appropriately applied as prior art.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Emily Bernhardt whose telephone number is 571-272-0664.

If attempts to reach the examiner by telephone are unsuccessful, the acting supervisor for AU 1624, James O. Wilson can be reached at 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.



Emily Bernhardt  
Primary Examiner  
Art Unit 1624